

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208673Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

(Including the Facility Review/Manufacturing Inspection Recommendation)

**NDA 208673
Review 2
Review Date: 11/8/16**

Drug Name/Dosage Form	Insulin Glargine and lixisenatide injection
Strength	100 units/mL and 33 mcg/mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
Applicant	Sanofi-Aventis US LLC

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>Original and Amendments</i>	<i>12/21/15, 3/02/16, 3/22/16, 5/02/16, 6/06/16, 6/16/16 and, 10/4/16</i>	<i>Quality (Module 3.2.P.3 and 1.1)</i>

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	N/A
Drug Product	Muthukumar Ramaswamy	New Drug Products II/ONDP
Process	Yuesheng Ye	Process Assessment/OPF
Microbiology	Maria Cruz-Fisher	Microbiology Assessment/OPF
Facility	Vipulchandra Dholakia	Inspectional Assessment/OPF
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management/OPRO
Application Technical Lead	Muthukumar Ramaswamy	New Drug Products II/ONDP
Facility	Vesa Vuniq	CDRH Compliance
ORA Lead	N/A	N/A
Environmental Analysis (EA)	Muthukumar Ramaswamy	New Drug Products II/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Sufficient information provided in NDA		LOA 2/10/15
	Type III					LOA 2/10/15
	Type III					LOA 2/20/15
	Type III					LOA 2/14/13
	Type III					12/28/06
	Type V			Adequate. Refer to microbiology review 12/09/15 and 9/3/15	LOA 1/30/09	
	Type V				LOA 5/11/15	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	062724	Lixisenatide
IND	105157	Insulin Glargine and Lixisenatide
IND	049078	Lantus Insulin Glargine
NDA	021081	Insulin Glargine (Lantus)
NDA	206538	Insulin Glargine (Tujeo)
NDA	208471	Lixisenatide

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Complete	Acceptable	4/26/16 and 4/27/16	Dr. Eshete
CDRH- Compliance	Complete	Acceptable, See review in DARRTS 4/21/16	3/15/16	Vesa Vuniq

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) for SOLIQUA 100/33 insulin Glargine and Lixisenatide injection is approval. Labeling comments are finalized through a multi-disciplinary review team managed by OND. CDRH Review of the pen injector information is complete. CDRH Reviewer has recommended approval of the pen injector device.

II. Summary of Quality Assessments

This NDA is a 505(b)(1) Type 1 application for a combination product containing an NME (Lixisenatide) and insulin Glargine. Insulin Glargine is approved under NDA 021081 and 206538. This NDA relies on available CMC information for drug substances insulin Glargine and Lixisenatide relies provided under NDA 021081 (insulin Glargine), 206538 (insulin Glargine), and 208471 (Lixisenatide), which is acceptable.

The established name for the product is insulin glargine and lixisenatide injection. The drug product is provided as prefilled pen in glass cartridges. Originally two fixed-ratio combination products containing 100 U of insulin Glargine and 33 or 50 µg of Lixisenatide per mL were proposed for glycemic control in adults with type 2 diabetes. Both products contained same amount of Insulin glargine (100 units) but different amounts of Lixisenatide (33 or 50µg) per mL. The NDA proposed two separate pen injectors to deliver the two drug products. Pen injectors were designated as Pen A and Pen B for use with high and low strength product.

Recently, the applicant has amended the NDA and now seeking approval for a single drug product containing 100 U of insulin Glargine and 33 µg of Lixisenatide per mL. The applicant is also proposing a new pen injector (Pen C) that is capable of delivering a dose range of 15-60 units of insulin Glargine. Pen C is a modification of the original pen injector proposed for use (Pen B). For additional details please refer to the correspondence between the Agency and the applicant (dated Aug. 8th, 2016, Aug. 9th 2016, and Aug. 11, 2016) and NDA amendment dated 10/4/16.

The proposed proprietary name for this product is SOLIQUA™ 100/33. Maximum daily dose information is 60 units. Please refer to package insert for additional information.

Drug Substance Quality Summary

Insulin glargine is a long acting form of human insulin analog produced by recombinant DNA technology. The Applicant has referenced NDA 021081 Lantus (insulin Glargine) for all CMC information on the drug substance and is adequate to support the proposed NDA.

Lixisenatide is a GLP-1 receptor agonist. Lixisenatide is a 44 amino acid synthetic peptide, amidated at the C-terminal position. Sanofi has referenced NDA 208471 for all CMC information on Lixisenatide including stability and storage conditions. Approval for NDA 208471 is pending.

B. Drug Product

The insulin glargine and lixisenatide injection is a sterile, clear, aqueous solution for subcutaneous injection. Originally the applicant proposed two fixed-ratio combination products containing 100 U of insulin Glargine and 33 or 50 µg of Lixisenatide per mL for glycemic control in adults with type 2 diabetes. Originally, the applicant also proposed two separate pen injectors (designated as Pen A and Pen B) to deliver the high and low strength product.

Recently, the applicant has amended the NDA (10/4/16) and now seeking approval for a single prefilled pen containing 100 U of insulin Glargine and 33 µg of Lixisenatide per mL. Per recent NDA amendment (10/4/16), the applicant has removed any reference to drug product containing 100U of insulin Glargine and 50 µg of Lixisenatide per mL from Section 3.2.P.1 Description and composition of the drug product, 3.2.P.8.2 Post-approval stability commitment and updated Sections 3.2.P.2.4 and 3.2.P.7 Pharmaceutical Development with additional CMC information for new pen injector. For additional details, please refer to the correspondence between the Agency and the applicant (dated Aug. 8th, 2016, Aug. 9th 2016, and Aug. 11, 2016) and NDA 208673 amendment dated 10/4/16.

Accordingly, the proposed proprietary name for the finished product is SOLIQUA™ 100/33. SOLIQUA™ 100/33 prefilled pen is capable of delivering 15-60 units of insulin glargine with 5-20 µg of Lixisenatide. Each mL of drug product contains 100U of insulin glargine (100U) and 33 µg of lixisenatide, 20 mg of glycerol (b) (4), 2.7 mg of metacresol, 3mg of methionine, and (b) (4) µg of zinc (b) (4) water for injection (b) (4). Hydrochloric acid and sodium hydroxide (b) (4) The drug product is filled in 3mL Type I glass cartridges and assembled in a pen injector.

The drug product composition, excipient specification, batch size, batch formula, manufacturing process and control information including microbiological control, batch analysis, drug product specification, analytical procedures, reference standards and stability data for insulin Glargine and Lixisenatide injection (33µg /100U per mL) are the same as the one filed in the original NDA submission. There are no changes to the drug product and device manufacturing sites. There are no changes to the primary container closure system (cartridge, plunger, and seal). There is no change in established control strategy to assure the quality of the product. All CMC information pertaining to insulin glargine and lixisenatide injection (100U/50µg per mL) provided in the original submission will be considered as supportive information for the proposed SOLIQUA 100/33 injection.

CMC information provided in the original NDA submission and its amendments (12/21/15, 3/02/16, 3/22/16, 5/02/16, 6/06/16, and 6/16/16) was reviewed by a review team consisting of various disciplines from Office Pharmaceutical Quality (OPQ) with additional input from CDRH Office of Compliance. The OPQ recommendation is based on CMC reviews from Dr. Muthukumar Ramaswamy (Drug product review dated 07/15/16), Dr. M. Cruz-Fischer (Microbiology review dated 7/13/16), Dr. Yuesheng Ye (Process review dated 7/14/16), Ms. Vesa Vuniqi (CDRH facilities review in DARRTS 4/21/16), and Dr. Vipulchandra Dholakia (Facilities review dated 7/11/16). OPQ CMC recommendation for this NDA is approval, (Refer to OPQ Integrated Quality Assessment dated 8/1/16 in Panorama under NDA 208673).

Information related to device design, design specification and dose accuracy was reviewed by CDRH reviewer (Mr. John McMichael). CDRH review concluded that the CMC information provided in the NDA is adequate to support the approval of the NDA in the context of device

constituent parts for the combination product. Refer to CDRH device review dated 10/31/16 in DARRTS.

Expiration Date & Storage Conditions Recommendation: Stability information available for the proposed product in cartridges and pen injector was reviewed by the drug product reviewer. An expiration period of 18 months is granted when stored at 2-8 °C, with an in-use period of up to 14 days at room temperature (below 86° F (30 °C) after first use for the finished product. Shelf-life is based on real-time stability data for the primary batches manufactured with the proposed commercial formulation.

SOLIQUA 100/33 should not be stored in the freezer or allowed to freeze. Discard SOLIQUA 100/33 if it has been frozen. Product should be stored away from light

C. Summary of Drug Product Intended Use: Insulin Glargine and Lixisenatide injection is intended for subcutaneous for subcutaneous use. See CDTL's memo for additional details.

LABEL: The proposed label for SOLIQUA™ 100/33 pen and carton are as follows:



**D. Life Cycle Knowledge Information - Final Risk Assessment**

Please refer to original OPQ IQA dated 8/1/16 for NDA 208673 in Panorama.

OVERALL ASSESSMENT AND SIGNATURES:

From CMC perspective, the proposed product is recommended for approval.

Muthukumar
Ramaswamy -S

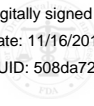
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Ramaswamy -S
DN: c=US, o=U.S. Government,
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Application Technical Lead Name and Date:



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Ramaswamy

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Recommendation: Approval

(Including the Facility Review/Manufacturing Inspection Recommendation)

**NDA 208673
Review 1
Review Date: 8/1/16**

Drug Name/Dosage Form	Insulin Glargine and lixisenatide injection
Strength	100 units/mL and 33 mcg/mL, 100 units/mL and 50 mcg/mL
Route of Administration	Subcutaneous injection
Rx/OTC Dispensed	Rx
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B. Other Documents: *IND, RLD, or sister applications*

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NDA	208471	Lixisenatide

2. CONSULTS

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Pharmacology/Toxicology	Complete	Acceptable	4/26/16 and 4/27/16	Dr. Eshete
CDRH- Compliance	Complete	Acceptable, See review in DARRTS 4/21/16	3/15/16	Vesa Vuniq

Sanofi has referenced NDA 208471 for all CMC information on Lixisenatide including stability and storage conditions. A retest period of (b) (4) mo. was recommended for Lixisenatide by NDA 208471 CMC reviewer team when stored at (b) (4) °C (b) (4). Approval for NDA 208471 is pending.

B. Drug Product

The insulin Glargine and Lixisenatide injection is a sterile solution for subcutaneous injection. The NDA proposes to utilize two fixed ratio combination products for use in adults with Type 2 diabetes: 2 units of insulin Glargine/μg of Lixisenatide and 3 units of insulin Glargine/μg of Lixisenatide. Each mL of drug product contains fixed amount of insulin Glargine (100U) and 33 μg of Lixisenatide (3U of Glargine /μg Lixisenatide) or 50 μg of Lixisenatide per mL (2U of Glargine /μg Lixisenatide). Both fixed ratio drug products contain 20 mg of glycerol (b) (4)%, 2.7 mg of metacresol, 3mg of methionine, (b) (4) μg of zinc (b) (4), and water for injection as inactive ingredients. Hydrochloric acid or sodium hydroxide (b) (4).

Excipients used in the product are known for use in pharmaceutical products. *Dr. Maria Cruz-Fischer has reviewed the preservative efficacy data and concluded that the proposed preservative level is adequate to the preserve the product.* Please refer to microbiology review dated 7/13/16 in Panorama.

The proposed fixed ratio products are filled in 3mL glass cartridges and packaged as pre-fill pens for commercial use. The primary (product-contact) container is a USP type 1 glass cartridge (3-mL), with a (b) (4) rubber disc on one end and a (b) (4) rubber plunger on the other end. Extractable and leachable data are reported in the NDA with supporting safety information. The compatibility of two active ingredients with the excipients as well as with the container closure components was demonstrated by the available stability data for the products. Please refer to drug product review for additional information.

Two separate pen injectors are proposed for delivering each of the FRC products. For example, 30 dose units dialed from pen injector, proposed for use with 2U insulin Glargine/μg Lixisenatide FRC product (Pen A) would contain 30 units of insulin Glargine and 15μg of Lixisenatide (Dose volume: 300μl). The same dose volume of 300μl, when dispensed with pen injector, proposed for use with 3U insulin Glargine/μg Lixisenatide FRC product (Pen B) using a setting of 30 dose units would deliver 30 units of insulin Glargine and 10μg of Lixisenatide. Pen A is intended for delivering a dose range of 10 to 40U of insulin Glargine and 5 to 20μg of Lixisenatide. Pen B is intended for delivering a dose range of 30 to 60 units of insulin Glargine and 10 to 20μg of Lixisenatide. Pen injector dials are blocked to avoid dispensing beyond maximum permitted dose per pen injector.

The caps and bodies of the two pen injector devices are differentiated by color (peach versus olive color pen). Similarly the product labels are differentiated by color. The prefilled pens are for single patient use only. The proposed pen injectors are similar to SoloStar pen delivery device. *For information related to device specification, including dose accuracy, please refer to separate review by CDRH Device Evaluation.*

Product differentiation strategy (2 different drug concentrations packaged in 2 different pen injectors), clinical dosing units (to make it clear to physicians that the product contains 2 active ingredients with different dosing regimens), and labeling information are issues determined by OND to be related to medication errors and are being handled by DMEPA and OND.

The proposed drug product manufacturing process utilizes standard operations used for the insulin injectable dosage form. (b) (4)

The following steps are critical during the manufacture of insulin Glargine and Lixisenatide injection: (b) (4)

The container closure system components proposed for use are the same as in approved Sanofi's insulin Glargine products. The manufacturing process was validated using three consecutive batches at commercial scale of (b) (4) L ((b) (4) cartridges). The proposed commercial manufacturing process and the process used for manufacturing clinical batches are similar. For detailed information on the manufacturing process and process control, please refer Dr. Yuesheng Ye's review in Panorama dated 7/14/16. Dr. Yuesheng Ye's review concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

Filled cartridges are integrated with pen injectors. Refer to CDRH facilities review in DARRTS 4/21/16 for additional details on manufacturing process flow for device assembly. Ms. Vesa Vuniq has recommended that manufacturing facilities associated with device assembly are acceptable.

The Applicant utilized risk assessment techniques to identify the critical quality attributes (CQA) of product and assessed the impact of manufacturing process parameters (Critical process parameters and incoming materials) on critical quality attributes. Appearance, Drug content/ Assay, Impurities/ degradants/ Aggregates, (b) (4) Sterility, Endotoxins, Particulate matter, pH, and Leachable/extractable are considered critical quality attributes of the drug product.

The critical attributes of the product are controlled through batch records instructions, process design, component specifications, in-process controls (b) (4) (b) (4) adequate (b) (4) processing techniques, and through adequate finished product specification. The proposed control strategy is adequate to assure the quality of the product.

Dr. Maria Cruz-Fischer has reviewed the drug product manufacturing process from microbiological controls perspective. Her review included information on (b) (4) processing, drug product specification for (b) (4), sterility, and endotoxin, (b) (4), container closure integrity studies, and post-approval stability commitment. Her review concluded that microbiological controls are adequate to support the NDA. Refer to CMC (Microbiology) review by Dr. M. Cruz-Fischer dated 7/13/16 in Panorama.

The proposed specifications are based on batches used in pre-clinical, clinical and registration stability studies and are in accordance with ICH Q6B recommendations, pharmacopeial and/or regulatory guidelines. The proposed drug product attributes are typical for protein drugs formulated as an injectable solution. The proposed specifications for insulin Glargine and its impurities conform to the specification approved for insulin Glargine injection (NDA 021081). The proposed acceptance criteria for lixisenatide and its impurities are (b) (4) than that proposed specification under Lixisenatide injection (NDA 208471).

Compared to NDAs 208471 (Lixisenatide) and 021081 (Lantus), there are no new degradants in the new combination drug product. Bioactivity of degradants correlating the potency of API by bioassay with the mass based HPLC assay is included in the NDA. Drug product reviewer has concluded that determination of potency based on mass based assay is acceptable.

Finished product (Pen injector) specification includes a test for dose accuracy and device functionality test. Please refer to CDRH Review for CDRH Device Evaluation.

Expiration Date & Storage Conditions: Stability information available for the proposed product in cartridges and pen injector was reviewed by drug product reviewer. An expiration period of 18 months is granted when stored at 2-8 °C, with an in-use period of up to 14 days at room temperature (below 86° F (30 °C) after first use for the finished product. Shelf-life is based on real-time stability data for the primary batches with the commercial formulation.

The facilities associated with the manufacturing of this product were reviewed by Dr. Vipulchandra Dholakia in consultation with CDRH compliance reviewer. Dr. Dholakia’s review concluded that there are no outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 208673 are found to be acceptable. Please refer to Dr. Vipulchandra Dholakia’s facilities review dated 7/11/16 in Panorama for details.

CMC Reviewer’s risk assessment for critical attributes is shown at the end of the review. The final risk assessment concluded that the final risk is low for the proposed product. No further mitigation necessary.

C. Summary of Drug Product Intended Use

Proprietary Name	See CDTL’s memo.
Non Proprietary Name of the Drug Product	Insulin Glargine and Lixisenatide injection
Non Proprietary Name of the Drug Substance	Insulin Glargine/Lixisenatide
Proposed Indication(s)	
Duration of Treatment	See CDTL’s memo.
Maximum Daily Dose	
Alternative Methods of Administration	

D. Life Cycle Knowledge Information

Final Risk Assessment - Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Drug content/ Assay	Formulation, Process, Container closure	H	(b) (4)	L	none
Impurities/ degradants/ Aggregates	Formulation, Process, Container closure	H		L	none
Appearance	Formulation, Process, Container closure	H		L	none

Sterility	Container closure Process	H	(b) (4)	L	none
Endotoxins	Container closure Process	H		L	
Particulate matter	Formulation	H		L	none
pH	Formulation	H		L	none
Leachable/ Extractables	Formulation, Process, Container closure	M		L	Reference the pharmaceutical development for container closure components
(b) (4)	Formulation, Process, Container closure	H		L	none

OVERALL ASSESSMENT AND SIGNATURES:

From CMC perspective, the proposed product is recommended for approval.

**Muthukumar
Ramaswamy -S**

Digitally signed by Muthukumar
Ramaswamy -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
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cn=Muthukumar Ramaswamy -S
Date: 2016.08.01 14:55:24 -04'00'

Muthukumar Ramaswamy, ONDP

August 1st, 2016

Application Technical Lead Name and Date: